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L42 0 FILE WSCA

TOTAL FOR ALL FILES
L43 7 HEMOGLOBIN (S) (POLYETHYLENE GLYCOL OR PEG?) (P) (THILOLAT OR IMINOTHIOLANE?)

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L44 6 DUP REM L43 (1 DUPLICATE REMOVED)

=> d l44 1-6 ibib abs

L44 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:454270 CAPLUS
DOCUMENT NUMBER: 147:47449
TITLE: Identification of the sites of deoxyhaemoglobin PEGylation
AUTHOR(S): Iafelic, Roberto; Cristoni, Simone; Caccia, Dario; Russo, Rosaria; Rossi-Bernardi, Luigi; Lowe, Kenneth C.; Perrella, Michele
CORPORATE SOURCE: Diparlimento di Scienze e Tecnologie Biomediche, LITA (Laboratorio Interdisciplinare di Tecnologie Avanzate), Universita degli Studi di Milano, Segrate(MI), 20090, Italy
SOURCE: Biochemical Journal (2007), 403(1), 189-196
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The 2-iminothiolane reaction with protein amino groups adds a spacer arm ending with a thiol group, which can be further treated with mols. carrying a maleimido ring. This approach is currently used for the preparation of a candidate 'blood substitute' in which human Hb (Hb) is conjugated with long chains of PEG [poly(ethylene glycol)]. To identify the thiolation sites by MS, we have carried out the reaction using deoxyHb bound to inositol hexaphosphate to protect some of the residues crucial for function and NEM (N-ethylmaleimide) to block and stabilize the thiol groups prior to enzymic digestion by trypsin and pepsin. Under the conditions for the attachment of 5-8 PEG chains per tetramer, the thiolated residues were Lys7, Lys11, Lys16, Lys56 and Lys139 and, with lower accessibility, Lys90, Lys99 and Lys60 of the α-chain and Lys8, Lys17, Lys59, Lys61 and Lys66 and, with lower accessibility, Lys65, Lys95 and Lys144 of the β-chain. The α-amino groups of α- and β-chains were not modified and the reaction of the Cysβ93 residues with NEM was minor or absent. After the modification with thiolane and NEM of up to five to eight lysine residues per tetramer, the products retained a large proportion of the properties of native Hb, such as low oxygen affinity, cooperativity, effect of the modulators and stability to autoxidn. Under identical anaerobic conditions, the conjugation of the thiolated Hb tetramer with five or six chains of the maleimido derivative of 6 kDa PEG yielded products with diminished cooperativity, Hill coefficient h = 1.3-1.5, still retaining a significant proportion of the effects of the modulators of oxygen affinity and stability to autoxidn. Co-operativity was apparently independent of the topol. distribution of the PEGylated sites as obtained by treating partly the thiolated protein with NEM prior to PEGylation [poly(ethylene glycol)ation].
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:1337827 CAPLUS
DOCUMENT NUMBER: 146:68521
TITLE: PEGylated hemoglobin and albumin for blood substitutes
INVENTOR(S): Acharya, Seetharama A.; Manjula, Belur N.
PATENT ASSIGNEE(S): Albert Einstein College of Medicine of Yeshiva University, USA
SOURCE: PCT Int. Appl., 59pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006135740	A1	20061221	WO 2006-US22463	20060609

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-689175P P 20050610

AB The present invention provides PEGylated Hbs and PEGylated albumins comprising polyethylene glycol (PEG) conjugated to Hb or to albumin, wherein the PEG is a maleimide PEG, an alkylamide PEG, an iodoacetamide PEG, a p-nitrothiophenyl PEG, a vinyl sulfone PEG, or a mixed disulfide PEG. The PEGylated albumins and PEGylated Hbs comprise polyethylene glycol (PEG) attached to a thiolated amino group of albumin or Hb, wherein the amino group is thiolated using dithiosulfosuccinimidyl propionate (DTSSP) or dithiosuccinimidyl propionate (DTSP) or dithiobispropionimidate. The invention also provides methods of preparing PEGylated Hbs and PEGylated albumins comprising (a) reacting Hb or albumin with a thiolating agent and with a PEGylating agent, and (b) capping unPEGylated reactive thiols of Hb or albumin with N-ethylmaleimide. The invention further provides compns. and blood substitutes comprising PEGylated Hbs and PEGylated albumins.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1016537 CAPLUS
DOCUMENT NUMBER: 144:337661
TITLE: Enhanced molecular volume of conservatively Pegylated Hb: (SP-PEG5K)6-HbA is non-hypertensive
AUTHOR(S): Acharya, Seetharama A.; Friedman, Joel M.; Manjula, Belur N.; Intaglietta, Marcos; Tsai, Amy G.; Winslow, Robert M.; Malavalli, Ashok; Vandegriff, Kim; Smith, Paul K.
CORPORATE SOURCE: Departments of Medicine, and of Physiology & Biophysics, Albert Einstein College of Medicine, Bronx, NY, USA
SOURCE: Artificial Cells, Blood Substitutes, and Biotechnology (2005), 33(3), 239-255
CODEN: ACBSDA
PUBLISHER: Taylor & Francis, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent studies have suggested that the "pressor effect" of acellular Hb is a consequence of perturbation of the macro- and microcirculatory system in multiple ways, and that PEGylation is an effective approach for controlling the same. In an attempt to confirm this concept, a new and simple thiolation mediated, maleimide chemical-based conservative PEGylation protocol has been developed to conjugate multiple copies of PEG-chains to Hb. This approach combines the high reactivity of maleimides towards thiols with the propensity of iminothiolane to derivatize the ε-amino groups of proteins into reactive thiol groups, with conservation of their pos. charge. One of the PEGylated products, namely (SP-PEG5K)6-HbA, that carries on an average six copies of PEG5000 chains per Hb, is non-hypertensive in hamster top load and in rat 50% exchange transfusion models. This hexa-PEGylated-Hb has (i) a hydro-dynamic volume corresponding to that of an oligomerized Hb of 256 kDa, (ii) a mol. radius of .apprx.6.8 nm, (iii) high oxygen affinity, (iv) lowered Bohr effect, and (v) increased viscosity and colloidal osmotic pressure. These properties of (SP-PEG5K)6-HbA are consistent with the emerging new paradigms for the design of Hb based oxygen carriers and confirm the concept that the "pressor effect" of Hb is a multifactorial event. The thiolation mediated maleimide chemical-based PEGylation protocol described here for the generation of (SP-PEG5K)6-Hb is simple, highly efficient, and is carried out under oxy conditions. The results demonstrate that a non-hypertensive PEG-Hb can be generated by conjugation of a lower number of PEG chains than previously reported.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:565112 CAPLUS
DOCUMENT NUMBER: 141:111584
TITLE: Preparation of modified hemoglobins for pharmaceutical uses
INVENTOR(S): Acharya, Seetharama A.; Manjula, Belur N.
PATENT ASSIGNEE(S): Albert Einstein College of Medicine of Yeshiva University, USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004058291	A1	20040715	WO 2003-US40407	20031218
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2511494	A1	20040715	CA 2003-2511494	20031218
AU 2003299700	A1	20040722	AU 2003-299700	20031218
EP 1585538	A1	20051019	EP 2003-799982	20031218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003017721	A	20051206	BR 2003-17721	20031218

CN 1741812	A	20060301	CN 2003-80109157		20031218
JP 2006514652	T	20060511	JP 2004-563778		20031218
IN 2005DN02820	A	20070119	IN 2005-DN2820		20050624
US 2006135753	A1	20060622	US 2005-538976		20051205
PRIORITY APPLN. INFO.:			US 2002-436149P	P	20021223
			WO 2003-US40407	W	20031218

AB The present invention provides a Hb mol. having at least PEG chains, wherein 2 of the PEG chains are bound to Cys-93 (ss) of Hb, and the remaining PEG chains are bound to thiol groups introduced on ε-NH2 of Hb. The present invention also provides a process for preparing a modified Hb mol. comprising the steps of: (a) reacting Hb with 8-15 fold excess of iminothiolane to form thiolated Hb; and (b) reacting the thiolated Hb with 16-30 fold excess of PEG functionalized with a maleimide moiety, to form the modified Hb. The oxygen affinity of PEG-Hb conjugates was determined

L44 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2003:678484 CAPLUS
DOCUMENT NUMBER:	139:219238
TITLE:	Methods and compositions for oxygen transport comprising a high oxygen affinity modified hemoglobin
INVENTOR(S):	Winslow, Robert M.; Vandegriff, Kim D.
PATENT ASSIGNEE(S):	Sangart, Inc., USA
SOURCE:	U.S. Pat. Appl. Publ., 25 pp., Cont.-in-part of U.S. Ser. No. 114,400. CODEN: USXXCO
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	2
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2003162693	A1	20030828	US 2003-340141		20030110
US 6844317	B2	20050118			
US 2003153491	A1	20030814	US 2002-114400		20020401
US 2005026816	A1	20050203	US 2004-925067		20040824
US 6974795	B2	20051213			
US 2005164915	A1	20050728	US 2005-88934		20050323
PRIORITY APPLN. INFO.:			US 2002-347741P	P	20020111
			US 2002-114400	A2	20020401
			US 2003-340141	A1	20030110
			US 2004-925067	A1	20040824

AB The present invention relates to blood products, and more particularly to compns. comprising a modified oxygenated Hb having a high affinity for oxygen and methods for making such compns. Such compns. according to the present invention have better stability to autoxidn. and superior oxygen carrying characteristics.

REFERENCE COUNT: 152 THERE ARE 152 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 6 OF 6 BIOTECHNO COPYRIGHT 2007 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER:	2003:36428335 BIOTECHNO
TITLE:	MP4, a new nonvasoactive PEG-Hb conjugate
AUTHOR:	Vandegriff K.D.; Malavalli A.; Wooldridge J.; Lohman J.; Winslow R.M.
CORPORATE SOURCE:	R.M. Winslow, 11189 Sorrento Valley Road, San Diego, CA 92121, United States. E-mail: rwinslow@sangart.com
SOURCE:	Transfusion, (01 APR 2003), 43/4 (509-516), 38 reference(s)

CODEN: TRANAT ISSN: 0041-1132
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2003:36428335 BIOTECHNO
AB BACKGROUND: Vasoconstriction has been an obstacle to clinical development of Hb-based O.sub.2 carriers. It is proposed that this limitation can be overcome by increasing molecular size and oxygen affinity. STUDY DESIGN AND METHODS: Surface-modified Hb (MP4) was designed, whose properties are consistent with the theory that cell-free Hb engages autoregulatory vasoconstrictive responses to Hb diffusion in the plasma space ("facilitated diffusion"). Human Hb was modified by reaction first with 2-iminothiolane to add sulfhydryl groups and then with monofunctional maleimide-activated 5-kDa PEG. RESULTS: MP4 was found to have a molecular weight of 90 kDa, a molecular radius increased relative to native Hb (9.3 ± 1.4 vs. 3.2 nm), high oxygen affinity (P.sub.5.sub.0 .apprx. 5-6 mmHg), and a Bohr effect approximately half that of native human Hb (-0.24Δlogp.sub.5.sub.0/ΔpH). At 4.2 g per dL in Ringer's lactate, its viscosity was 2.5 cP, and its oncotic pressure was 50 mmHg. The t.sub.5.sub.0 of .sup.1.sup.4C-MP4 in rats was approximately 24 hours. No significant elevation in mean arterial pressure was observed. CONCLUSION: MP4 appears to be free of a pressor effect, a major limitation to the development of a safe and effective RBC substitutes in the past.

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